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**Ethnic differences in intrahepatic lipid and its association with hepatic insulin sensitivity and insulin clearance between men of Black and White ethnicity with early type 2 diabetes**

**Short title: Ethnicity, hepatic fat and type 2 diabetes**

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## ABSTRACT

Intrahepatic lipid (IHL) is linked with reduced hepatic insulin sensitivity and insulin clearance. Despite their high risk for type 2 diabetes (T2D), there have been limited investigations of these relationships in Black populations. We investigated these relationships in 18 White European (WE) and 18 Black West African (BWA) men with T2D <5 years. They underwent magnetic resonance imaging to quantify IHL, a hyperinsulinemic-euglycemic clamp with [6,6  $^2\text{H}_2$ ] glucose infusion to assess hepatic insulin sensitivity and a hyperglycemic clamp to assess insulin clearance. BWA men had lower IHL than WE men (3.7 (5.3) vs 6.6 (10.6) %,  $p=0.03$ ). IHL was inversely associated with basal hepatic insulin sensitivity in WE but not BWA men (BWA:  $r=-0.01$ ,  $P=0.96$ ; WE:  $r=-0.72$ ,  $P=0.006$ ) with a significant interaction by ethnicity ( $P_{\text{interaction}}=0.05$ ), however, IHL was not associated with % suppression of endogenous glucose production by insulin in either ethnicity. IHL showed a trend to an association with insulin clearance in BWA only (BWA:  $r=-0.42$ ,  $P=0.09$ ; WE:  $r=-0.14$ ,  $P=0.58$ ). The lack of association between IHL and hepatic insulin sensitivity in BWA men indicates IHL may play a lesser detrimental role in T2D in BWA men.

**KEY WORDS:** Ethnicity, hepatic fat, insulin sensitivity, insulin clearance, African, lipotoxicity

49    **ABBREVIATIONS**

50    ALT: Alanine aminotransferase

51    BSA: Body surface area

52    BWA: Black West African

53    HbA1C: Glycated hemoglobin

54    IHL: Intrahepatic lipids

55    MRI: Magnetic resonance imaging

56    SAT: Subcutaneous adipose tissue

57    VAT: Visceral adipose tissue

58    WE: White European

## INTRODUCTION

Black populations are disproportionately affected by type 2 diabetes (T2D) with 2-3 times greater prevalence compared to white populations<sup>1</sup> despite typically having lower intrahepatic lipids (IHL) and visceral adipose tissue (VAT)<sup>1,2</sup>. IHL is usually elevated in individuals with T2D and is inversely associated with both hepatic insulin sensitivity and insulin clearance<sup>3</sup>. Consistently, insulin clearance has been shown to be lower in Black populations compared to White populations<sup>4</sup>. However, investigations of ethnic differences in hepatic insulin sensitivity have shown inconsistent findings<sup>5-7</sup>. We have previously reported similar hepatic insulin sensitivity but lower insulin clearance in Black West African (BWA) compared to White European (WE) men<sup>8,9</sup>. Despite the literature reporting ethnic differences in IHL, hepatic insulin sensitivity, and insulin clearance between Black and White populations, these have not previously been investigated in a single study to understand their relationships and how ethnicity impacts on these in the development of T2D in Black populations. Therefore, our aim was to investigate ethnic differences in IHL and its relationship with hepatic insulin sensitivity and insulin clearance in BWA and WE men with early T2D.

## **METHODS**

This investigation was conducted as part of the South London Diabetes and Ethnicity Phenotyping study (Soul-Deep)<sup>10</sup>. Data on metabolic parameters for 92% of the present cohort have been previously reported<sup>8,9</sup>, the present analyses relate to the whole cohort in whom relevant data were available. Participant recruitment and data collection took place April 2013 to January 2015. The study was approved by the London Bridge National Research Ethics Committee (12/LO/1859); all participants provided written informed consent.

### **Participants**

Participants were recruited from primary care practices in London and deemed eligible to participate if they were 1) 18-65 years old, 2) BMI of 25-40 kg/m<sup>2</sup>, 3) self-reported WE or BWA ethnicity, 4) diagnosis of T2D (less than 5 years), and 5) treated with lifestyle and/or metformin only. Further details of eligibility criteria are published in the protocol<sup>10</sup>. Participants attended all assessments after an overnight fast. If on metformin, participants were instructed to cease taking it for 7-days prior to each visit. Physical activity was measured as hours per day of moderate intensity activity using accelerometry watches worn for 4 consecutive days (MotionWatch 8.0, CamTech).

### **Magnetic Resonance Imaging**

A Dixon-based MRI sequence was used on a 1.5 Tesla Siemens scanner to obtain images for the quantification of IHL and VAT. Participants were scanned lying supine on a spine RF coil with body phased array RF coils placed over the chest, abdomen and pelvis. While abdominal images were acquired participants were instructed to complete three 17-second breath-holds. From each participant, contiguous, axial T1-weighted gradient-echo images (repetition time: 6.77ms; echo times: 4.77ms (in-phase), 2.39ms (out-of-phase), flip angle: 10°) each with a slice thickness of 3mm were acquired, from which water and fat images were produced. Images were analyzed using HOROS v1.1.7 ([www.horosproject.org](http://www.horosproject.org); accessed 21/10/2017). IHL was

measured by selecting two abdominal MRI images representing the superior and inferior parts of the liver. Four circular regions of interest (ROIs) in identical positions were placed within the liver tissue of each pair of water and fat images (supplementary material, Figure 1). ROIs were positioned to include the posterior, anterior, medial and lateral sections of the liver. ROI areas ranged from 20 to 30cm<sup>2</sup>, intending to cover as large an area of liver as possible while avoiding blood vessels, bile ducts and artefacts. Using the formula: %IHL = (F/(F+W))\*100, where F is the pixel signal intensity of the fat image and W is the pixel signal intensity of the water image, the hepatic fat fraction was calculated in each ROI and IHL was calculated as the mean of all 8 ROIs. Total abdominal VAT and body SAT (neck to knee, excluding arms) was determined using an automated MRI analysis technique (Klarismo Ltd., London, UK) as previously described<sup>11</sup>.

### **Clamp assessments**

Whole-body insulin sensitivity (M-value) during the high dose insulin infusion (40 mU m<sup>-2</sup> BSA min<sup>-1</sup>), hepatic insulin sensitivity (% suppression of endogenous glucose production (EGP) during the low dose insulin infusion (10 mU m<sup>-2</sup> BSA min<sup>-1</sup>) and basal hepatic insulin sensitivity index) were measured using a two-step hyperinsulinemic-euglycemic clamp with the infusion of [6,6 <sup>2</sup>H<sub>2</sub>] glucose, according to previously described methodology<sup>9</sup>. The basal hepatic insulin sensitivity index was calculated as the reciprocal of the product of basal EGP rate (mmol/BSA min<sup>-1</sup>) and fasting insulin concentration (pmol/l). To assess and model insulin clearance, each participant underwent a hyperglycemic clamp, described in detail elsewhere<sup>8</sup>.

### **Statistical analysis**

Ethnic differences were determined using independent samples t-test for normally distributed variables or a Mann-Whitney test for variables that could not be log transformed to normal. ANCOVA was used, with VAT, BMI and age as separate covariates, to investigate ethnic differences in IHL and VAT. Correlations were assessed using Pearson's correlation; partial



124 correlation was used to investigate associations while adjusting for VAT, BMI and age.  
125 Significance of an interaction by ethnicity was assessed using multiple regression with  
126 ethnicity\*logIHL used as an interaction term. Analyses were conducted with SPSS version  
127 25.0;  $P \leq 0.05$  were considered statistically significant.

## RESULTS

### Participant characteristics

The 18 BWA and 18 WE men were well-matched for age and BMI, Table 1. The BWA men had significantly lower IHL and total VAT mass, Table 1 (Figure 2, supplementary data). After adjustment for BMI, the ethnic differences in VAT remained significant ( $P=0.008$ ) but not for IHL ( $P=0.18$ ). After adjustment for VAT, there were no ethnic differences in IHL (WE: 6.07 (SE 1.16) vs BWA: 5.56 (SE 1.16) %,  $P=0.70$ ). Non-alcoholic fatty liver disease, defined as liver fat above 5% determined by Dixon-MRI<sup>12</sup>, was present in 33% of BWA men compared to 67% of WE men ( $P=0.047$ ).

### Metabolic characteristics

There were no ethnic differences in whole-body insulin sensitivity (M-value) or hepatic insulin sensitivity, expressed as % suppression of EGP during the low dose insulin infusion, Table 1; consistent with earlier findings we reported from a smaller sample from this cohort<sup>9</sup>. However, there was a trend towards higher basal hepatic insulin sensitivity index in the BWA men, Table 1. Insulin clearance was not different between the BWA and WE men (Table 1), again consistent with our earlier report<sup>8</sup>.

### Relationships between IHL and insulin sensitivity

Relationships between IHL and the measures of insulin sensitivity are presented in Figure 1 (A, B and C). The inverse associations between IHL and both whole-body insulin sensitivity (M-value) and basal hepatic insulin sensitivity reached statistical significance in only the WE men. In multiple regression analysis a significant ethnicity interaction was found in the relationship between IHL and basal hepatic insulin sensitivity ( $P_{\text{interaction}}=0.05$ ); no other significant ethnicity interactions were found. There were no changes in the associations after adjustment for VAT, BMI or age except for the relationship between IHL and M-value which reduced in significance in WE men after adjustment for BMI ( $P=0.13$ ) (supplementary data).

153 **Relationships between IHL and insulin clearance**

154 Relationships between IHL and insulin clearance, are presented in Figure 1 (D). IHL was  
155 inversely associated with insulin clearance, which neared significance, in BWA but not WE  
156 men; partial correlation adjusting for VAT reduced the significance of this relationship (BWA:  
157  $r=-0.41$ ,  $P=0.11$ ; WE:  $r=-0.29$ ,  $P=0.27$ ); no significant ethnicity interaction was found  
158 ( $P_{\text{interaction}}=0.40$ ).

## CONCLUSIONS

In this study of White European and Black West African men with early T2D, we investigated ethnic differences in hepatic fat and its relationship with hepatic insulin sensitivity and insulin clearance. Consistent with published data<sup>13</sup>, BWA men had lower IHL and VAT. We found additional ethnic differences in relationships between IHL and hepatic insulin sensitivity and insulin clearance whereby in WE men, IHL was inversely related to basal hepatic insulin sensitivity and whole-body insulin sensitivity, which was not the case in BWA men. In BWA men we found a trend towards an inverse relationship between IHL and insulin clearance which was not found in the WE men. Our findings suggest that IHL is implicated in the metabolic derangements of the liver in T2D differently according to ethnicity. To our knowledge, this is the first study to investigate relationships between IHL and insulin clearance in a Black population; the trend towards an inverse relationship in BWA but not WE men suggests that the reduction of insulin clearance may be modulated differently depending on ethnicity. Despite relationships between IHL and whole-body insulin resistance being commonly reported, the mechanisms that link the two are less understood. Current investigations show an excess of liver fat leads to accumulation of lipid intermediates causing hepatic mitochondrial dysfunction, inflammation and increased VLDL-TAG production which may result in hepatic and systemic insulin resistance<sup>14</sup>. Our finding of IHL being inversely associated with basal hepatic insulin sensitivity and whole-body insulin sensitivity which reached significance in WE but not BWA men may indicate the above detrimental effects of lipid intermediates occurring to a greater extent in WE men. There was no relationship between IHL and suppression of EGP in either ethnic group. This could indicate a decreased effect of IHL on hepatic insulin sensitivity in the insulin stimulated state compared to the basal state in WE men. To our knowledge only one other study has investigated the relationship between IHL and hepatic insulin sensitivity using the

hyperinsulinemic-euglycemic clamp with infusion of isotopically labelled glucose<sup>6</sup>; they found that IHL was associated with hepatic insulin sensitivity in obese Black South African women but not in obese White South African women, which contradicts our findings. There are several potential explanations for this, such as glycemic state; our study included participants with T2D whereas the South African women were normal glucose tolerant. The disparities may also be due to gender differences as there is consistent evidence demonstrating that the phenotype of T2D differs by gender within populations of African descent<sup>15</sup>.

The presence of NAFLD was comparable to that reported in other large multi-ethnic cohorts<sup>16</sup> and was significantly lower in the BWA men. One of the main theories that explains how IHL accumulates is the “portal theory”, which states that excess VAT releases free fatty acids directly into the portal vein, subsequently depositing as IHL<sup>17</sup>. Our study may support the portal theory as after adjustment for VAT, IHL no longer differed by ethnicity, suggesting that the lower IHL in BWA men may be driven by lower VAT. Indeed, ethnic differences in the mechanisms of SAT expansion may explain the differences we found in VAT as others have suggested<sup>18</sup>; however, we did not directly measure adipogenesis in our study which may be an implication for further research.

The strengths of this study include the use of the rigorous hyperinsulinemic-euglycemic clamp method combined with the infusion of [6,6 <sup>2</sup>H<sub>2</sub>] glucose to determine both whole-body and hepatic insulin sensitivity. However, our study is not without its limitations. Our sample size is relatively small; in these secondary analyses we may not have sufficient power to reliably detect ethnic differences. Our measurement of insulin clearance does not differentiate hepatic from extrahepatic insulin clearance, rather it is a measure of whole-body insulin clearance. However, it has been shown that approximately 80% of endogenous insulin is degraded in the liver<sup>3</sup>. Our WE men had greater statin use which may have resulted in lower hepatic fat accumulation and reduced the ethnic discrepancies due to the lipid lowering effects of statins.

209 Another limitation is studying only men with T2D, however previous studies have mostly  
210 focused on women, due to the greater prevalence of T2D in Black women compared to men.  
211 Our study redresses this.

212 In conclusion, our study demonstrates ethnic differences in the relationships between IHL and  
213 metabolic parameters of the liver. The lack of inverse association between IHL and basal  
214 hepatic insulin sensitivity in the BWA men, found in the WE men, suggests that fasting hepatic  
215 insulin resistance occurs independently of IHL in BWA men. However, the reduction of insulin  
216 clearance may be influenced by IHL more so in Black men with T2D compared to White men.

## **Author contributions**

L.M.G. formulated the research question and designed the study, supervised data collection and interpretation, and performed the minimal modelling analysis. S.A.A. formulated the research question and designed the study, supervised data collection and interpretation. J.L.P. formulated the research question, designed the study, and provided statistical advice. A.M.U. formulated the research question and designed the study. K.G.M.M.A. supervised data collection and interpretation. C.M. coordinated the study and data acquisition, and performed the metabolic assessments. T.B. undertook data acquisition and analysis. G.C.E. coordinated MRI data acquisition. B.W. and H.S. undertook MRI data analysis. F.S. and N.J. undertook data acquisition. R.B. and L.B. performed the modelling analysis. O.H. undertook data analysis, statistical analysis and drafted the manuscript. All authors contributed to the intellectual content and reviewed the final version of the submitted manuscript.

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247 Louise Goff is the guarantor of this work, had full access to all the data, and takes full  
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252 **Duality of interests:** The authors declare that there is no duality associated with this  
253 manuscript.



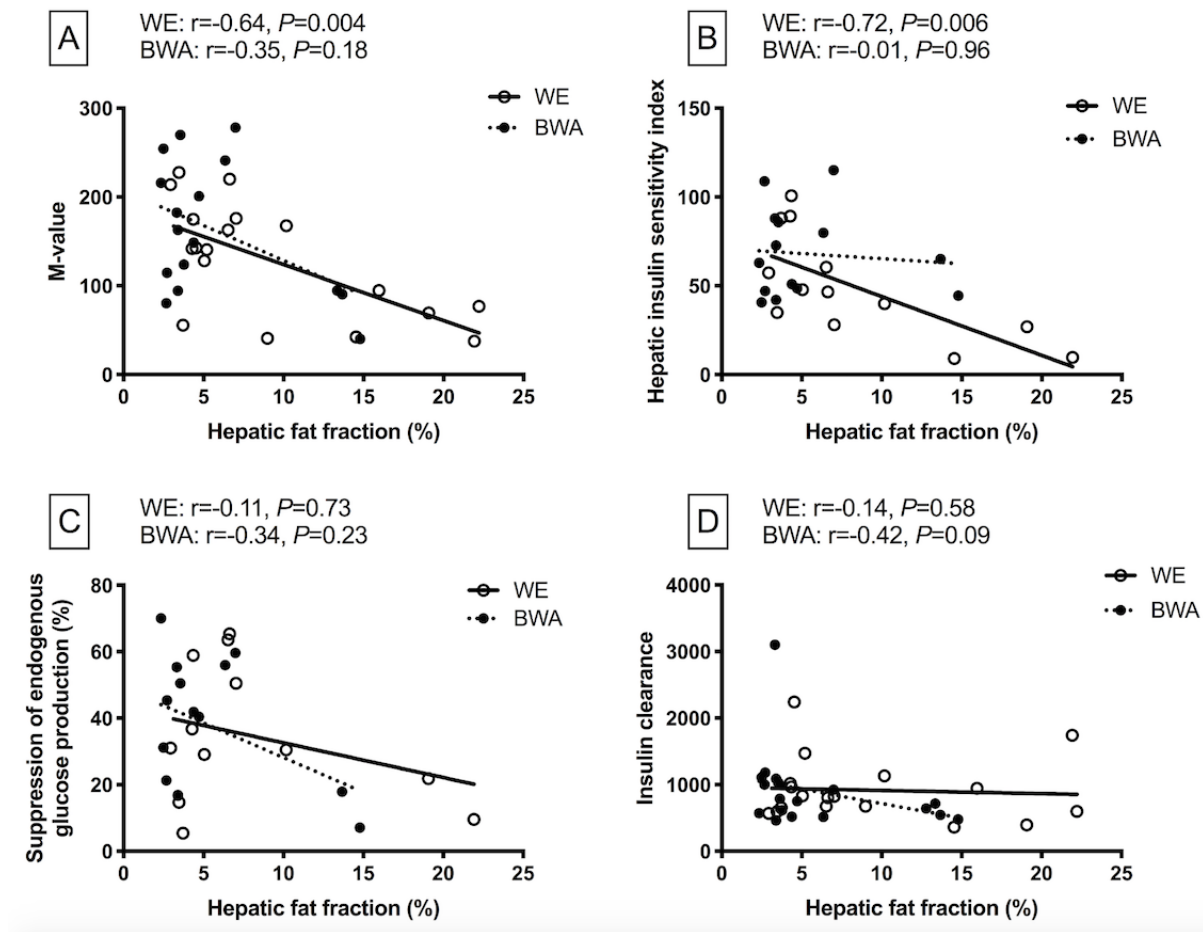
254 **Table 1: Clinical and metabolic characteristics of Black West African and White**  
255 **European men**

	<b>BWA</b> <b>(n=18)</b>	<b>WE</b> <b>(n=18)</b>	<b>P</b>
Age (years)†	54.9 (9.3)	58.5 (6.3)	0.67
Weight (kg)	92.3 ± 12.3	99.8 ± 16.7	0.14
BMI (kg/m <sup>2</sup> )	29.8 ± 3.5	31.5 ± 4.1	0.18
Waist circumference (cm)	104.9 ± 10.2	111.9 ± 13.0	0.08
SAT (neck to knee) (kg)‡	12.6 (10.5-15.2)	14.6 (12.2-17.6)	0.24
VAT, total (kg) <sup>a</sup>	3.99 ± 1.54	6.09 ± 2.46	<b>0.006</b>
IHL (%)†	3.7 (5.3)	6.6 (10.6)	<b>0.03</b>
Diabetes duration (years)†	3.0 (2.2)	3.0 (1.3)	0.42
Statin use§	10/18	16/18	<b>0.026</b>
Fasting glucose (mmol/l)	6.63 ± 0.67	6.88 ± 1.38	0.50
HbA1c (%)	6.67 ± 0.68	6.64 ± 0.70	0.90
ALT‡ (IU/l)	26.7 (21.8-32.5)	31.2 (25.7-37.7)	0.24
Systolic BP (mm Hg)	136.7 ± 13.8	130.9 ± 14.2	0.22
Diastolic BP (mm Hg)†	89.0 (8.7)	83.0 (12.5)	0.06
Total cholesterol (mmol/l)	4.11 ± 0.73	4.27 ± 0.70	0.50
LDL-cholesterol (mmol/l)	2.32 ± 0.56	2.28 ± 0.66	0.85
HDL-cholesterol (mmol/l)	1.18 ± 0.38	1.19 ± 0.25	0.92
Triglyceride (mmol/l)†	1.05 (0.70)	1.60 (1.25)	<b>0.03</b>
Moderate activity time (hours/day) <sup>c</sup>	2.1 ± 0.66	1.9 ± 0.90	0.74
<b>Metabolic characteristics</b>			
M value (mg/m <sup>2</sup> BSA min <sup>-1</sup> ) <sup>d</sup>	162.0 ± 75.0	128.5 ± 63.7	0.17
Hepatic basal insulin sensitivity index ((mmol/m <sup>2</sup> BSA min pmol l <sup>-1</sup> ) <sup>-1</sup> ) <sup>e</sup>	68.0 ± 24.6	49.1 ± 29.4	0.09
Suppression of endogenous glucose production (%) <sup>e</sup>	37.9 ± 19.5	34.7 ± 20.7	0.70
Average insulin clearance (mL/m <sup>2</sup> BSA min <sup>-1</sup> )†	732.8 (505.7)	814.6 (450.2)	0.61

256 Data presented as mean ± SD or geometric mean (95% CI) for log transformed data (§) or median (interquartile  
257 range) for non-parametric data (†) or number of participants for ordinal data (§). *P* values determined using  
258 independent samples t-tests for normally distributed data, Mann-Whitney test for non-parametric data or chi-

259 squared test for ordinal data. N for <sup>a</sup>WE=17, BWA=17; <sup>b</sup>WE=17, BWA=16; <sup>c</sup>WE=10, BWA=7; <sup>d</sup>WE=18,  
260 BWA=16; <sup>e</sup>WE=12, BWA=14.

261 Abbreviations: ALT, alanine aminotransferase; BP, blood pressure; BWA, Black West African; HbA1c, glycated  
262 hemoglobin; HDL, high density lipoprotein; IHL, intrahepatic lipid; LDL, low density lipoprotein; SAT,  
263 subcutaneous adipose tissue; VAT, visceral adipose tissue; WE, White European.



**Figure 1:** Relationships between hepatic fat fraction and (A) hepatic insulin sensitivity index (basal) ( $\text{mmol/m}^2 \text{BSA min pmol l}^{-1}$ ), (B) suppression of hepatic glucose production (%), (C) whole-body insulin sensitivity (M-value) ( $\text{mg/m}^2 \text{BSA min}^{-1}$ ), and (D) insulin clearance ( $\text{mL/m}^2 \text{BSA min}^{-1}$ ) in WE and BWA men. Relationships between hepatic insulin clearance and (E) suppression of endogenous glucose production, and (F) hepatic insulin sensitivity index (basal) in WE and BWA men. Black circles with dotted line = BWA men, white circles with solid line = WE men.

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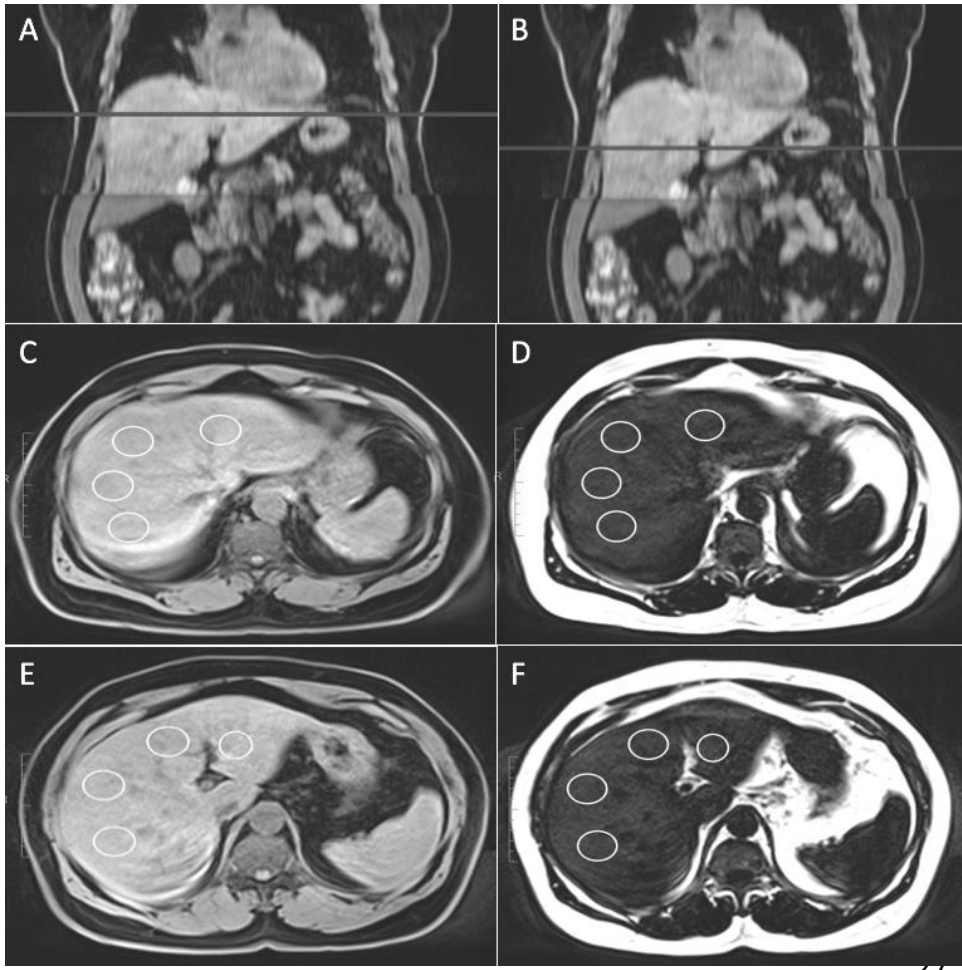
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**Supplementary data:**

**Table 1:** Pearson's correlation and partial correlation coefficients showing relationships between hepatic fat fraction and measures of insulin sensitivity and insulin clearance in white European and black West African men

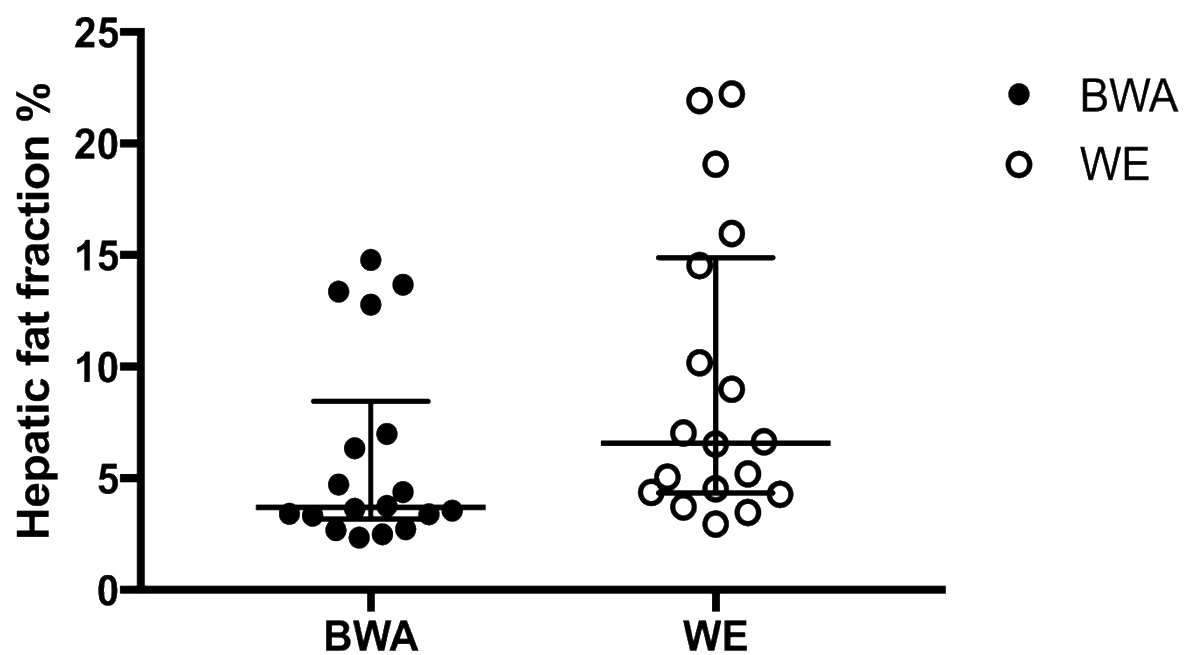
	WE		BWA	
	<b>r</b>	<b>p</b>	<b>r</b>	<b>p</b>
M-Value	<b>-0.64</b>	<b>0.004</b>	-0.35	0.18
Adjusted for age	<b>-0.07</b>	<b>0.003</b>	-0.39	0.15
Adjusted for BMI	-0.38	0.13	-0.05	0.85
Adjusted for VAT	<b>-0.56</b>	<b>0.02</b>	-0.06	0.85
Hepatic insulin sensitivity index	<b>-0.72</b>	<b>0.006</b>	-0.01	0.96
Adjusted for age	<b>-0.70</b>	<b>0.01</b>	-0.12	0.96
Adjusted for BMI	<b>-0.60</b>	<b>0.04</b>	-0.16	0.60
Adjusted for VAT	<b>-0.73</b>	<b>0.01</b>	0.35	0.26
% Suppression of endogenous glucose production	-0.11	0.73	-0.34	0.23
Adjusted for age	-0.12	0.72	-0.51	0.07
Adjusted for BMI	-0.04	0.91	-0.21	0.50
Adjusted for VAT	-0.03	0.93	-0.02	0.95
Insulin clearance	-0.14	0.58	-0.42	0.09
Adjusted for age	-0.15	0.57	-0.44	0.07
Adjusted for BMI	0.14	0.59	-0.27	0.29
Adjusted for VAT	-0.29	0.27	-0.41	0.11

Abbreviations: BMI, body mass index; BWA, black West African; VAT, visceral adipose tissue; WE, white European



**Figure 1:** Quantification of intrahepatic lipids by selection of two axial MRI images with regions of interest positioned on the right and left lobes of the liver as well as the posterior, anterior, medial and lateral sections.

Panel A shows a coronal MRI image with the horizontal line depicting the position of axial images C and D. Panel B shows a coronal MRI image with the horizontal line depicting the position of axial images E and F. Panel C shows 4 circular regions of interest on an axial abdominal MRI water image on the superior section of the liver. Panel D shows the axial abdominal MRI fat image that corresponds to image C with 4 identical regions of interest. Panel E shows 4 circular regions of interest on an axial abdominal MRI water image on the inferior section of the liver. Panel F shows the axial abdominal MRI fat image that corresponds to image E with 4 identical regions of interest.



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41 **Figure 2:** Boxplot of hepatic fat fraction in White European (WE) and Black West African  
42 men (BWA) with early type 2 diabetes matched for both age and BMI

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